

Topoisomerase-I Inhibitors in Gynaecologic Tumours

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Abstract

Topoisomerase inhibitors have been studied using various dose schedules in the treatment of refractory or recurrent gynaecologic cancers. Response rates are between 13% and 20%. Main toxic effects are haematologic and gastrointestinal. The latter remains problematic. Radiotherapy, alkylate, platinum analogs and topoisomerase II inhibitors are currently being studied in combination with camptothecins.

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Introduction

Topoisomerases are essential nuclear enzymes with a multiplicity of cellular functions involving DNA replication, RNA transcription, mitosis, and chromosome condensation.^{1,2} Two classes have been identified: the class I topoisomerases, named "I" because they induce single-strand breaks and reunions of the DNA double helix, and the class II topoisomerases, named "II" because they induce double-strand breakage and reunion reactions within the DNA double helix.³ These enzymes catalyze the interconversion of various topological isomers of DNA.⁴⁻⁶

Type I topoisomerase (topo-I) is a monomeric nuclear enzyme of about 100 kDa.⁷ Its gene has been mapped to chromosome 20q12-13.2.^{8,9} The topo-I monomer forms a covalent adduct with the genomic DNA and relaxes the DNA supercoils by transiently cleaving a single strand of duplex DNA.¹⁰ The formation of covalent complexes of topo-DNA fragments, called "cleavable complexes", induces uncoiling of the DNA molecule, which permits the polymerase action to replicate the DNA strand. Subsequent enzymatic DNA reunion is also catalyzed by topoisomerase-I.¹¹ Recently, topo-I has been also shown to interact with the TATA-binding protein.¹² The catalysis reaction performed by topo-I does not depend on additions of adenosine triphosphate. The energy for the rearrangement is probably derived from the reaction between the topo-I enzyme and the 3'-phosphoryl end of the free DNA strand.¹³

Camptothecin (CPT), an alkaloid from the tree, *camptotheca acuminata* (Nyssaceae), is the parent com-

pound of topotecan (TPT), irinotecan (CPT-11), 9 aminocamptothecin (9AC), 9 nitrocamptothecin (9NC), and other analogs.¹⁴ The 2 initial compounds are water soluble derivatives of camptothecin, and the two latter ones, are water insoluble. The active forms of the camptothecins contain a closed lactone ring. The ring open and closed forms are in equilibrium which is pH dependent.¹⁵ At physiology pH, most of the CPT is in carboxylate form. In human serum, the area under the curve (AUC) of the lactone form is between 0% and 16% of the AUC of both forms combined.¹⁶ Current research is focusing on increasing the stability the lactone form of newer analogs.

The pre-clinical activity of CPT and its analogs has been demonstrated in several models including gynaecologic tumours. Using a subrenal capsule assay, CPT-11 tested in two cervical cell lines showed growth suppressive effects of over 50%.¹⁷ CPT analogs also augmented the activity of cisplatin, 5-fluorouracil and VP-16 in HST-1, a human squamous cell carcinoma cell line.¹⁸ The synergy seen with cisplatin may be due to a stabilization of cisplatin DNA adducts.¹⁹ These compounds also appear to have radiosensitization properties in small cell and lung adenocarcinoma cell lines.^{20,21} The addition of recombinant tumour necrosis factor (rh-TNF) to CPT-11 in several gynaecologic cancer cell lines demonstrated synergy.^{22,23}

In addition, some analogs are prodrugs, and need to be metabolized for optimal activity. For example, SN38 is the active metabolite of CPT-11. A carboxylesterase catalyzes the conversion of CPT-11 to SN-38 (7-ethyl-10-

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hydroxycamptothecin). Carboxylesterase activity in 179 fresh human tumours representing 18 different tumour types ranged from 0.009 to 1.274 with a median value of 0.125 $\mu\text{mol}/\text{min}/\text{mg}$ protein. The tumour types containing the highest carboxylesterase activity are lymphoma, small cell lung cancer, endometrial cancer, and mesothelioma. There was a statistically significant correlation between tumour carboxylesterase activity and antitumour activity as determined by the tumour colony forming unit assay ($P < 0.05$). Carboxylesterase activity may be an important correlate of CPT-11 cytotoxicity.²⁴

Systemic Therapy for Refractory Gynaecologic Disease

Chemotherapy for recurrent or refractory gynaecologic cancers usually consists of single agents. Reported response rates range from 15% to 50% with complete responses being rare. Cisplatin or carboplatin is considered the most active single drug. Combination chemotherapy has been attempted in numerous trials. High response rates are documented even in heavily treated patients. However, the durability of responses is short, and survival is not improved over single agent treatments. Furthermore, when randomized trials are performed comparing single agent therapy to combination, the results do not favour combinations. Thus there is a significant need for newer approaches, such as topoisomerase-I inhibitors.

Cervical Cancer

Only CPT-11 and TPT have been tested in this disease.

1) Irinotecan (Table I)

There have been 5 trials of CPT-11 as a single agent in cervical cancer refractory to platinum-based therapy. The first phase II trial in the United States used a schedule of 125 mg/m²/week for four weeks followed by two weeks of rest. Forty-two patients, with platinum refractory cervical cancer aged 24 to 59 years with a median

age of 44 years (range 24 to 59 years), were treated with a median of two cycles (range 1 to 14). All patients had failed prior chemotherapy. The response rate was 21% with a median time to response of 6 weeks and a duration of 12 weeks. The major dose limiting side-effects were nausea and vomiting (45%), diarrhoea (24%) and myelosuppression (36%). Myelosuppression did not significantly decrease with dose reduction, whereas gastrointestinal side-effects did. In this patient population, CPT-11 has significant clinical activity. Haematologic and gastrointestinal side-effects remain problematic,²⁵ but the drug is worth further evaluation.

In the second trial conducted in the United States by the Gynecologic Oncology Group (GOG), 54 patients were treated for recurrent or refractory disease. Most had received prior radiotherapy and 12 had also received chemotherapy. Among 49 evaluable patients, a 14% remission rate, including one complete response, was observed. Thirty-nine per cent of patients experienced a gastrointestinal toxicity grade 3 or 4. It was concluded that CPT-11 had modest activity with moderate toxicity and should be studied with cisplatin in the future.²⁶

The European Organization for Research and Treatment of Cancer (EORTC) has conducted a trial of CPT-11 in chemotherapy naive patients with cervical cancer. Patients were stratified according to measurable disease outside previously irradiated area (Group A) or within the radiated area (Group B). The dose was 350 mg/m² given every three weeks. In Group A there was a 24% response rate, while in Group B there were no responses, for an overall response rate of 15%. The duration of response was 6+ months. Two toxic deaths occurred secondary to myelosuppression, diarrhoea and dehydration. Further studies were recommended to better define the gastrointestinal side-effects.²⁷

Japanese investigators tested a schedule of 100 mg/m² weekly for four doses in 24 patients. Five patients (21%)

TABLE I: TRIALS OF IRINOTECAN IN CERVICAL CANCER

Dose	Schedule	Total	CR	PR	Total	Ref.
			% (No. Pts.)	% (No. Pts.)	% (No. Pts.)	
125 mg/m ²	Weekly x 4	42	2 (1)	19 (8)	21 (9)	25
125 mg/m ²	Weekly x 4	49	2 (1)	10 (5)	12 (6)	26
350 mg/m ²	Q 3 weeks					
	Group A	21	5 (1)	19 (4)	24 (5)	27
	Group B	13	0 (0)	0 (0)	0 (0)	
100 mg/m ²	Weekly x 4	24	8 (2)	13 (3)	21 (5)	28
150 mg/m ²	Q 2 weeks x 3	31	10 (3)	16 (5)	26 (8)	29
Total		180	4 (8)	14(25)	18(33)	

CR: complete remission; PR: partial remission; pts: patients

responded.²⁸ Among 31 patients entered on a schedule of 150 mg/m² every 2 weeks for 3 doses, 26% responded.²⁹ The majority of patients in both groups had prior radiotherapy and chemotherapy. Myelosuppression and gastrointestinal side-effects were significant and deaths were reported. No recommendation was made regarding further study. However, chemotherapy combinations with topoisomerase-I inhibitors are currently under study in Japan.

2) Topotecan

Twenty-nine patients with cervical cancer were given TPT, a semisynthetic analog of camptothecin, by a 30-min intravenous daily infusion for five consecutive days at a dose of 1.2 mg/m²/day. All patients had measurable disease by imaging studies. Seven patients had no prior chemotherapy, and 22 prior chemotherapy regimens. Histologic types were squamous cell carcinoma (21 patients) and adenocarcinoma (4 patients). Four partial responses (overall response rate, 18%) were observed in patients with squamous cell carcinoma. The major side-effects were haematologic with Grade 3 and 4 leukopenia seen in 70% and 35% of patients, respectively. Grade 3 and 4 thrombocytopenia were seen in 50% and 25% of patients, respectively, and Grade 3 anaemia in 80% of patients. All the above haematologic toxic effects were controllable, and all non-haematologic side-effects were mild ($\leq$ Grade 2), except for Grade 3 anorexia in 5% of the patients.³⁰

3) Combination with topoisomerase I inhibitors

Sugiyama et al³¹ performed a dose finding study of CPT-11 and cisplatin combination. CPT-11 was given on days 1, 8 and 15. Cisplatin was administered only on day 1. Cycles were repeated every 28 days. The recommended dose for further studies was 60 mg/m² of cisplatin and 60 mg/m² of CPT-11. Among the 17 patients treated, 6 had a major response. A phase II trial of the same combination has been presented this year at the ASCO meeting. A 68% overall response rate has been reported.³²

Ovarian Cancer

Many topoisomerase I inhibitor analogs have been studied in this disease.

1) Topotecan (Table II)

Topotecan showed activity in platinum refractory ovarian cancer in phase I studies.³⁹ The first Phase II study of topotecan in patients with platinum refractory epithelial ovarian cancer who had no prior taxane treatment has shown a median response rate of 14%, stable disease in 60% of patients, and an overall survival of 10 months.³³ In patients with potentially platinum sensitive disease, the median response rate was 20%, stable disease was 50%, and overall survival was 12 months.³⁴ Some patients treated with paclitaxel after failure of topotecan responded, while others did not. This led to the impression that taxanes and topotecan may be non-cross resistant.³³

Once taxanes' use became widespread topotecan studies included patients who failed prior taxane therapy. Interestingly, there was no difference in anticancer activity regardless of prior taxane treatment. These promising results led to a phase III trial, comparing the activity of topotecan and paclitaxel among patients with recurrent or refractory ovarian cancer. Topotecan 1.5 mg/m²/day as a 30-min infusion for 5 days every 21 days was compared to paclitaxel 135 mg/m² infused over 3-hour every 21 days.⁴⁰ The response rate was 20.5% in topotecan treated patients and 13.2% in paclitaxel treated patients ($P = 0.138$). Among platinum refractory patients the response rates for topotecan and paclitaxel were 13.3% and 6.7% ($P = 0.303$), while among potentially platinum sensitive the response rates were 28.8% and 20% ($P = 0.213$) respectively. The median duration of response to topotecan and paclitaxel was 32 and 20 weeks, respectively ($P = 0.222$) and median time to progression was 23 and 14 weeks, respectively ($P = 0.002$). The median survival was 61 weeks for topotecan and 43 weeks for paclitaxel ($P = 0.515$). Neutropenia was more frequent in the topotecan treated patients (79%) versus paclitaxel treated patients (23%).

TABLE II: STUDIES OF TOPOTECAN IN RECURRENT OVARIAN CANCER

	Evaluable pts.	Platinum refractory (%)	Taxane pre-treated (%)	Response rate (%)	Stable disease (%)	Median survival (mo)	Ref.
Prior platinum and no prior taxane							
Kudelka et al	28	100	0	14	60	10	33
Creemers et al	92	67	0	16.3	21	NR	34
Armstrong et al	16	90	0	25	56	NR	35
Eisenhauer et al	33	NR	0	12	NR	NR	36
Prior platinum and prior taxane							
Swisher et al	28	93	93	14	36	6	37
Gordon et al	200	NR	100	13.5	NR	10	38

NR: not reported

After progression with the original drug some of the patients received the alternative one. Five of 53 patients achieved a partial response with topotecan (9.4%) after failing paclitaxel and one of 37 patients achieved a complete response with paclitaxel (2.7%) after failing topotecan. However, one does wonder why in this study the response rate to paclitaxel was so poor and the neutropenia so mild.⁴¹

Pharmacokinetic studies of iv TPT have demonstrated rapid plasma clearance. Therefore, there may be a significant pharmacologic advantage to administer TPT into the peritoneal cavity. A Phase I trial of ip topotecan given as a 24-hour infusion in D5W at pH 3.5 was performed with treatments repeated every 28 days when feasible. Ten patients with platinum-refractory ovarian cancer were treated starting at a dose of 3 mg/m². Dose-limiting toxicity was grade IV neutropenia which occurred in 2 of 6 cycles given at the MTD of 4 mg/m². Other observed toxicities included grade 4 anaemia and grade 3 thrombocytopenia. All 5 patients with clinically evident ascites had a reduction of ascites with symptomatic relief lasting up to 3 months. The recommended phase II dose was 3 mg/m².⁴²

2) Irinotecan

The experience with irinotecan in ovarian cancer is less extensive than that of topotecan. An early phase II study showed 21% response rate among 14 patients with ovarian cancer.²⁸ In a late phase II study the investigator noted a response rate of 23% (12/52).²⁹ The schedules used were 100 mg/m² once weekly and 150 mg/m² every other week. Both were felt by the investigators to be clinically useful.

3) GG211

GG211 is a water-soluble totally synthetic camptothecin analog with broad pre-clinical antitumour activity. It was administered by a 72-hour continuous infusion every 3 weeks at doses ranging from 0.25 to 2.0 mg/m²/day (phase I study). Activity was observed in a patient with ovarian cancer at the 0.5 mg/m²/day dose. The response lasted 13 weeks. Furthermore, decreases in CA 125 levels were noted in additional patients. Phlebitis occurred with peripheral infusions making the use of central venous catheters necessary. Otherwise the drug was well tolerated with other toxicities including mild nausea and vomiting, fatigue, headache, and alopecia. Myelosuppression was observed at all dose levels, and correlated with the dose. Severe side-effects were mainly observed in patients who had received extensive prior therapy.⁴³

4) 9NC

Another analog that has been tested in a phase II study is 9NC. 9NC is a water-insoluble derivative of CPT

which had demonstrated activity against ovarian cancer in a phase I study.⁴⁴ Phase I 9NC was administered orally at a dose of 1.5 mg/m²/day for 4 consecutive days every week in a follow up phase II study. A response rate of 7% was observed in a highly refractory population of patients with epithelial ovarian cancer. Disease stabilization occurred in 30% of patients and lasted for a median of 22 weeks. The main side-effects were gastrointestinal and haematologic, rendering prolonged administration difficult.⁴⁵

5) 9AC

Phase II studies of 9AC are currently under way. Preliminary results are similar to those reported with other analogs.

Uterine Cancer

There are no published studies of topoisomerase-I inhibitors in this disease.

Conclusions

The topoisomerase-I inhibitors have not been extensively studied in some gynaecologic cancers. Single agent activity is definite but modest with all analogs of the first generation. Most investigators recommend combination studies with cisplatin, and such studies are underway. Preliminary results show greater efficacy but toxic effects are also increased. Laboratory data show potentially interesting interactions with radiotherapy and cytokines. Such findings need further refinement with the conduct of correlative clinical studies.

The second generation of CPT derivatives includes compounds that maintain a high lactone profile in human plasma. Examples of such compound include DX895IF⁴⁶ and esters of CPT.⁴⁷ These compounds are currently tested in phase I trials.

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